

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ³: C07D 213/75, A61K 31/395, 31/44, C07D 401/12, 405/12	A1	(11) International Publication Number: WO 94/21611 (43) International Publication Date: 29 September 1994 (29.09.94)
(21) International Application Number: PCT/GB94/00455 (22) International Filing Date: 9 March 1994 (09.03.94) (30) Priority Data: 9305672.9 19 March 1993 (19.03.93) GB (71) Applicant (for all designated States except US): JOHN WYETH & BROTHER LIMITED [GB/GB]; Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): CLIFFE, Ian, Anthony [GB/GB]; Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH (GB). IFILL, Anderson, Decourtney [GB/GB]; Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH (GB). (74) Agents: BROWN, Keith, John, Symons et al.; Wyeth Laboratories, Patent & Trademarks Dept., Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH (GB).		(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, HU, JP, KP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: AMIDE DERIVATIVES AS 5-HT _{1A} LIGANDS <div style="display: flex; justify-content: space-around; align-items: flex-start;"> <div style="text-align: center;"> $\text{R}^1\text{NR}^4\text{CH}_2\text{CR}^2\text{N}(\text{R}^1)\text{COR}^3$ <p>(I)</p> </div> <div style="text-align: center;"> <p>(A)</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: flex-start; margin-top: 20px;"> <div style="text-align: center;"> <p>(B)</p> </div> <div style="text-align: center;"> <p>(D)</p> </div> </div>		
(57) Abstract Amide derivatives of formula (I) wherein R ¹ is a mono or bicyclic heteroaryl radical, R ² is cycloalkyl, R ³ , R ^{3'} and R ⁴ each represent hydrogen or lower alkyl, and R ⁵ is a group of formula (A) or (B) or (C): R ⁵ -CH ₂ -CH ₂ - or (D) or (E): R ⁵ OCH ₂ CHOHCH ₂ - or (F): R ⁵ OCH ₂ CH ₂ - and their pharmaceutically acceptable salts are 5-HT _{1A} binding agents and may be used, for example, as anxiolytics.		

FOR THE PURPOSES OF INFORMATION ONLY

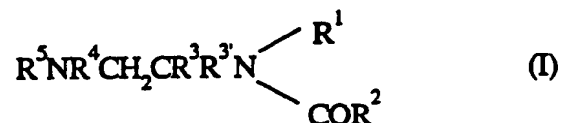
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

AMIDE DERIVATIVES AS 5-HT_{1A} LIGANDS

5 This invention relates to novel amide derivatives, to processes for their preparation, to their use and to pharmaceutical compositions containing them. The novel compounds act on the central nervous system by binding to 5-HT receptors (as more fully explained below) and hence can be used as medicaments for treating humans and other mammals.

10 The novel compounds of the invention are those of general formula (I)



and the pharmaceutically acceptable salts thereof.

15 In formula (I)

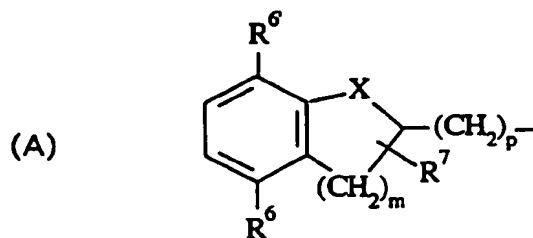
R^1 is a mono or bicyclic heteroaryl radical,

R^2 is cycloalkyl,

20

R^3 , $\text{R}^{3'}$ and R^4 each represent hydrogen or lower alkyl,

and R^5 is a group of formula



25

where X is $-(\text{CH}_2)_n-$, $-\text{OCH}_2-$ or $-\text{SCH}_2-$, m is 0 or 1, n is 1, 2 or 3 and p is 0 or 1 such that $(m + p)$ is 1 and that $(m + n)$ is 1, 2 or 3,

-2-

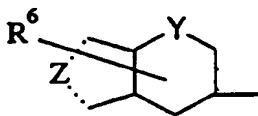
R⁶ is hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, (lower)alkoxycarbonyl, carboxamido, nitro, cyano, amino, (lower)alkylamino, di(lower)alkylamino or (lower) alkylcarbonyl,

- 5 R^{6'} is hydrogen or halogen when X is $-(CH_2)_n-$ and R^{6'} is hydrogen when X is $-OCH_2-$ or $-SCH_2-$,

R⁷ is hydrogen or lower alkyl

10 or

(B)



where Y is $-O-$, $-S-$ or $-CH_2-$,

15

Z represents a heteroaromatic ring fused on to the non-aromatic ring containing the Y group

- 20 and R⁶ is as defined above and one or more R⁶ groups may be attached to the heteroaromatic ring and/or the non-aromatic ring

or

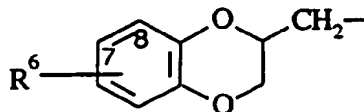
(C)



- 25 where R⁸ is a monocyclic or bicyclic heteroaryl group

or

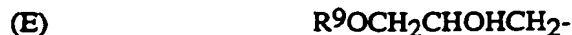
(D)



30

where R⁶ is as defined above and the indicated 7, 8 positions may optionally be fused with a heteroaromatic ring or a further aromatic ring

or



where R^9 is a mono or bicyclic aryl or bicyclic heteroaryl group

or



where R^9 is as defined above.

10

The term "lower" as used herein means that the radical referred to contains 1 to 6 carbon atoms. Preferably such radicals contain 1 to 4 carbon atoms. Examples of "lower alkyl" radicals are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and isopentyl.

15

Examples of cycloalkyl groups are groups containing 3 to 8 carbon atoms e.g. cyclopentyl, cyclohexyl and cycloheptyl.

20

When used herein "aryl" means an aromatic radical having 6 to 12 carbon atoms (e.g. phenyl or naphthyl) which optionally may be substituted by one or more substituents. Preferred substituents are lower alkyl, lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy), halogen (e.g. chlorine), halo(lower)alkyl (e.g. trifluoromethyl), nitro, nitrile, amido, (lower)alkoxycarbonyl, amino, (lower)alkylamino and di(lower)alkylamino.

25

The term "heteroaryl" refers to an aromatic radical containing one or more (e.g. 1, 2 or 3) hetero ring atoms (e.g. oxygen, nitrogen, sulphur) and which may be optionally substituted by one or more substituents. Examples of suitable substituents are given above in connection with "aryl" radicals. The heteroaryl radical may, for example, contain 5 to 10 ring atoms. Unless specified otherwise the heteroaryl radical is preferably mono- or bicyclic. A monocyclic radical may, for example, contain 5 to 7 ring atoms. Preferably the hetero ring contains a nitrogen atom with or without one or more further hetero atoms. Examples of heteroaryl groups include, for example, pyridinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl and indolyl each of which may be optionally substituted as mentioned above.

35

When a "heteroaromatic ring" is fused on to a non-aromatic ring (as in formula B) or is fused on to an aromatic ring (as in formula D) the "heteroaromatic ring" may be a fused "heteroaryl" group where heteroaryl is defined above.

Examples of the preferred meanings of the various substituents in formula (I) are given below:

5 R¹ is pyridinyl, particularly 2-pyridinyl,

R² is cyclohexyl,

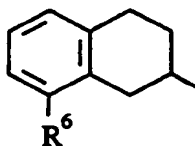
R³ is hydrogen and R^{3'} is hydrogen or lower alkyl (e.g. methyl),

10

R⁴ is preferably hydrogen, methyl or propyl,

A is preferably a group of formula:

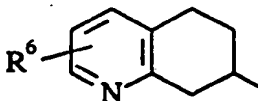
15



where R⁶ is as defined above, particularly lower alkoxy,

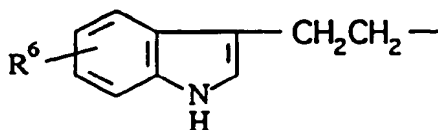
B is preferably a group of formula:

20



where R⁶ is as defined above,

25 C is preferably a group of formula

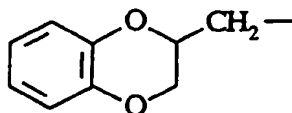


where R⁶ is as defined above, particularly lower alkoxy,

30

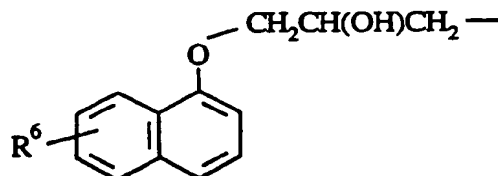
D is preferably a group of formula

-5-



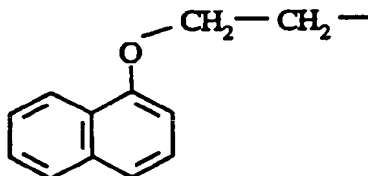
E is preferably a group of formula

5



where R⁶ is as defined above,

10 F is preferably a group of formula



15 The compounds of the invention may be prepared by methods known in the art from known starting materials or starting materials that may be prepared by conventional methods.

One method of preparing the compounds of the invention comprises the reductive amination of a compound of formula

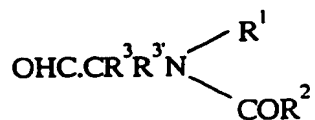
20



(II)

(where R⁵ and R⁴ are as defined above)

25 with an aldehyde of formula



(III)

(where R^1 , R^2 , R^3 and $R^{3'}$ are as defined above) eg by reacting the compounds of formula (II) and (III) in the presence of a reducing agent (e.g. a hydride reducing agent such as sodium triacetoxyborohydride) or reacting the compounds of formula (II) and (III) together followed by reduction, eg using catalytic hydrogenation.

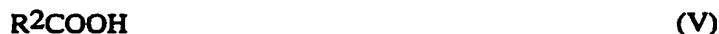
5

A second method of preparing the compounds of the invention comprises acylating an amine of formula



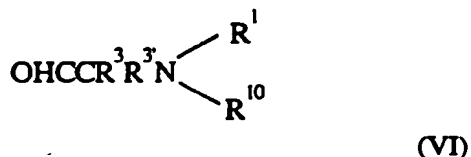
10

(where R^1 , R^3 , $R^{3'}$, R^4 and R^5 are as defined above) with an acid of formula



- 15 where R^2 is as defined above or with an acylating derivative thereof. Examples of acylating derivatives include the acid halides (e.g. chlorides) azides, anhydrides, imidazolides (e.g. obtained from carbonyldiimidazole), activated esters or O-acyl ureas obtained from a carbodiimide such as a dialkylcarbodiimide particularly cyclohexylcarbodiimide. In the compound of formula (IV) R^4 is preferably lower alkyl. If it is
20 desired to prepare a compound of the invention in which R^4 is hydrogen it may be necessary to use a compound of formula (IV) in which R^4 is an amine protecting group and to remove the protecting group after the acylation reaction.

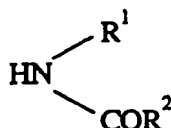
- 25 The starting compounds of formula (IV) may be prepared by reductive amination of a compound of formula (II) above with an aldehyde of formula



- 30 where R^1 , R^3 , $R^{3'}$ are as defined above and R^{10} is hydrogen or, preferably, an amino protecting group (e.g. an urethane such as tert-butoxycarbonyl), in presence of a reducing agent (e.g. a hydride reducing agent such as sodium triacetoxyborohydride) followed by deprotection of the amino group. When R^{10} is, for example, tert-butoxycarbonyl the protecting group may be removed by treatment with trifluoroacetic
35 acid or dilute hydrochloric acid.

-7-

A third method of preparing the compounds of the invention comprises alkylating an amide of formula

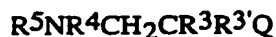


(VII)

(where R¹ and R² are as defined above) with an alkylating agent providing the group



The alkylating agent may be, for example a compound of formula



(VIII)

(where R³, R^{3'}, R⁴ and R⁵ are as defined above and Q is a leaving group such as a halogen (e.g. bromine) or an ester (e.g. a tosylate or trifluoromethylsulphonate). In this process R⁴ is preferably lower alkyl.

A fourth method of preparing the compounds of the invention comprises heteroaryllating a compound of formula



(IX)

(where R², R³, R^{3'}, R⁴ and R⁵ are as defined above) with a compound providing the heteroaryl group R¹. For example the reaction can be carried out with a fluoro compound of formula R¹F in the presence of a strong non-nucleophilic base (e.g. lithium diisopropylamide). When R¹ = 2-pyridyl or R¹ = 4 pyridyl, the reaction is preferably carried out with a 2-fluoro- or 4- fluoropyridine-N-oxide followed by deoxygenation of the product pyridine-N-oxide with a reducing agent such as phosphorus trichloride.

If in any of the other processes mentioned herein, a substituent on the group R⁵ is other than the one required the substituent may be converted to the desired substituent by known methods. A substituent on R⁵ may also need protecting against the conditions

under which the reaction is carried out. In such a case the protecting group may be removed after the reaction has been completed.

5 The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be
10 with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

15 Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic, p-toluenesulphonic, oxalic and succinic acids.

The compounds of the invention contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be for example, racemates or optically active forms. The optically active forms can be obtained
20 by resolution of the racemates or by asymmetric synthesis.

The compounds of the present invention possess pharmacological activity. In particular, they act on the central nervous system by binding to 5-HT receptors. The compounds particularly bind to receptors of the 5-HT_{1A} type. The compounds of the invention can
25 be used for the treatment of CNS disorders, such as anxiety in mammals, particularly humans. They may also be used as antidepressants, antipsychotics, hypotensives and as agents for regulating the sleep/wake cycle, feeding behaviour and/or sexual function and for treating cognition disorders.

30 The compounds of the invention are tested for 5-HT_{1A} receptor binding activity in rat hippocampal membrane homogenate by the method of B S Alexander and M D Wood, J Pharm Pharmacol, 1988, 40, 888-891.

35 The compounds are tested for 5-HT_{1A} receptor antagonism activity in a test involving the antagonism of 5-carboxamidotryptamine in the guinea-pig ileum in vitro (based upon the procedure of Fozard et al, Br J Pharmac. 1985, 86, 601P).

The invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid or liquid.

Solid form compositions include powders, granules, tablets, capsules (e.g. hard and soft gelatine capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, e.g. from 0.03 to 99%, preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included.

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution, alcohols, e.g. glycerol and glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl

-10-

myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration.

5 Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it can be administered orally either in liquid or solid composition form.

10 Preferably the pharmaceutical composition is in unit dosage form e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged composition, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquid. The unit dosage form can be, for example, a capsule or tablet.

15 quantity of the active ingredient in unit dose of composition may be varied or adjusted from 0.5 mg or less to 750 mg or more, according to the particular need and the activity of the active ingredient.

The following Examples illustrate the invention:

20

Example 1

5 N-(3-(N'-(1,2,3,4-Tetrahydro-8-methoxynaphth-2-yl)methylamino)-2-propyl)-N-(2-pyridinyl)cyclohexanecarboxamide

A stirred suspension of potassium hydride, 35 wt. % suspension in mineral oil (0.01 mol) in dimethylformamide (DMF) (100 ml) is treated dropwise under argon with N-(3-(N'-(1,2,3,4-tetrahydro-8-methoxynaphth-2-yl)methylamino)-2-propyl)-N-(2-pyridinyl)amine (0.01 mol) in DMF (100 ml), after 1 h treated dropwise with cyclohexanecarbonyl chloride (0.01 mol), after 1 h treated dropwise with water (500 ml), acidified with 2N-HCl, washed with hexane (3 x 300 ml), basified with 2N-NaOH, and extracted with ethyl acetate (3 x 300 ml). The extracts are washed with brine (500 ml), dried (Na₂SO₄), and evaporated in vacuo. The residue is purified by chromatography [silica; ethyl acetate - ethanol (200:1)] to give the product as a colourless solid.

Example 2

20

N-(3-(N'-(5,6,7,8-Tetrahydroquinolin-7-yl)methylamino)-2-propyl)-N-(2-pyridinyl)cyclohexanecarboxamide

This compound is prepared using the procedure of Example 1 with N-(3-(N'-(5,6,7,8-tetrahydroquinolin-7-yl)methylamino)-2-propyl)-N-(2-pyridinyl)amine in place of the amine reagent.

Example 3

30

N-(3-(N'-(2-(3-(5-Methoxyindolyl)ethyl)methylamino)-2-propyl)-N-(2-pyridinyl)cyclohexanecarboxamide

35 This compound is prepared using the procedure of Example 1 with N-(3-(N'-(2-(3-(5-methoxyindolyl)ethyl)methylamino)-2-propyl)-N-(2-pyridinyl)amine in place of the amine reagent.

Example 4

N-(3-(2-(2,3-Dihydro-1,4-benzodioxinyl)methylamino)-2-propyl)-
5 N-(2-pyridinyl)cyclohexanecarboxamide

A solution of 2,3-dihydro-1,4-benzodioxin-2-ylmethylamine (0.01 mol) and N-(1-(1-formyl)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide (0.011 mol) in 1,2-dichloroethane (50 ml) is treated with sodium triacetoxyborohydride (0.015 mol) under
10 argon. Acetic acid (0.01 mol) is added and the mixture stirred for 18 h, washed with water (2 x 50 ml), dilute aqueous sodium carbonate (50 ml), and water (50 ml), dried (MgSO₄), and evaporated *in vacuo*. The residue is purified by chromatography (alumina; ethyl acetate - methanol) to give the product.

15

Example 5

N-(4-Aza-6-hydroxy-7-(1-naphthyloxy)-2-heptyl)-
20 N-(2-pyridinyl)cyclohexanecarboxamide

This compound is prepared using the procedure of Example 4 with 2-hydroxy-3-(1-naphthyloxy)-1-propylamine in place of the amine component.

25

Example 6

N-(4-Aza-6-(1-naphthyloxy)-4-propyl-2-hexyl)-
30 N-(2-pyridinyl)cyclohexanecarboxamide

This compound was prepared following the procedure of Example 1 with N-(4-aza-6-(1-naphthyloxy)-4-propyl-2-hexyl)pyridine-2-amine instead of the amine reagent.

Example 7

5 N-(2-(N'-(2-(2,3-Dihydro-1,4-benzodioxinyl)methyl)methylamino)ethyl-
 N-(2-pyridinyl)cyclohexanecarboxamide

A mixture of N-(2-(N'-(2-(2,3-dihydro-1,4-benzodioxinyl)methyl)-
methylamino)ethyl)pyridine-2-amine (2.20g, 7.35 mmol), cyclohexanecarbonyl chloride
(1.08g, 7.35 mmol), 4-(dimethylamino)pyridine (catalytic amount) and diisopropyl-
10 ethylamine (0.95g, 7.35 mmol) in dichloromethane (30 ml) was stirred over the
weekend. The reaction mixture was diluted with dichloromethane (30 ml), washed with
water (30 ml), dried (Na₂SO₄) and concentrated under reduced pressure to afford an oil.
The crude oil was chromatographed on alumina, eluting with ethyl acetate:hexane (1:1 to
3:1) to give an oil (1.22g). A sample of the oil (0.50g) was dissolved in diisopropylether
15 and acidified with ethereal hydrogen chloride to afford the hydrochloride salt of the title
compound as an off-white solid (0.39g) mp = 83.5-88°C.
¹H NMR δ_H (200 MHz; CDCl₃) 0.8 - 1.8 (10H, m) and 2.22 (1H, t) (cyclohexyl); 2.31
(3H, s, NMe); 2.6 (2H, m) and 3.9 (2H, m) (NCH₂CH₂N); 2.7 (2H, m, NCH₂); 4.1 - 4.3
(3H, m, OCH₂CH); 6.7 - 6.9 (4H, m, benzodioxan); 7.2 - 7.3 (2H, m, pyridine H3 and
20 H5); 7.74 (1H, dt, pyridine H4); and 8.51 (1H, dd, pyridine H6).

Example 8

25 N-(2-(N'-(7-(5,6,7,8-Tetrahydroquinolinyl))methylamino)ethyl)-N-(2-
 pyridinyl)cyclohexanecarboxamide

30 (a) N-(2-Pyridinyl)-2-(N'-(7-(5,6,7,8-tetrahydroquinolinyl))methylamino)acetamide

A solution of N-methyl-5,6,7,8-tetrahydroquinoline -7-amine (7.08g, 12.8 mmol), N-(2-
pyridyl)-2-chloroacetamide (2.19g, 12.8 mmol) and diisopropylethylamine (1.66g, 12.8
mmol) in N,N-dimethylformamide (70 ml) was stirred at room temperature overnight.
The reaction mixture was poured into water (200 ml) and washed with ethyl acetate (2 x
35 100 ml). The combined organic phases were washed with brine (100 ml), water (100
ml), dried (MgSO₄) and concentrated to afford an oil. The crude oil was
chromatographed on alumina, gradient eluting with ethyl acetate:hexane (1:1) and ethyl
acetate to give the title compound of step (a) as an oil (2.67g).

(b) N-Methyl-N-(2-(2-pyridinylamino)ethyl)-5,6,7,8-tetrahydroquinoline-7-amine

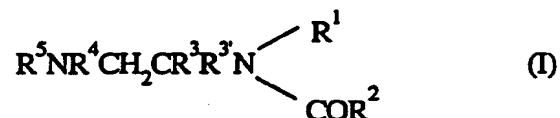
A solution of the product of step (a) (1.70g, 5.74 mmol) and borane-methyl sulphide
5 complex in toluene (2.0M, 8.60 ml, 17.2 mmol) in tetrahydrofuran (15 ml) was heated
under reflux for 3 h. Methanol (5 ml) was added dropwise to the cooled (0°C) reaction
mixture which was subsequently concentrated under reduced pressure. The residue was
dissolved in a mixture of water (10 ml) and concentrated hydrochloric acid (10 ml). The
solution was heated under reflux for 40 min, cooled (0°C) and basified with aqueous
10 sodium hydroxide (2M). The basic solution was washed with ethyl acetate (3 x 30 ml)
and the combined organic phases washed with brine (30 ml), water (30 ml), dried
(MgSO₄) and concentrated to give the title compound of step (b) as an oil (1.26g).

(c) N-(2-(N'-(7-(5,6,7,8-Tetrahydroquinoliny))methylamino)ethyl)-N-(2-
15 pyridinyl)cyclohexanecarboxamide

A solution of the product of step (b) (1.26g, 4.46 mmol), cyclohexanecarbonyl chloride
(0.65g, 4.46 mmol), diisopropylethylamine (0.58g, 4.46 mmol) and a catalytic amount of
4-N,N-dimethylaminopyridine in dichloromethane (15 ml) was stirred overnight at room
20 temperature. The separated organic phase was washed with water (15 ml), dried
(MgSO₄) and concentrated to afford an oil (1.28g). The crude oil was chromatographed
on alumina, gradient eluting with ethyl acetate:hexane (5:4) and ethyl acetate to give an
oil. The oil was dissolved in ethyl acetate and acidified with ethereal hydrogen chloride
to afford an off-white hygroscopic solid. The solid was redissolved in isopropanol,
25 concentrated and triturated with ethyl acetate to afford the dihydrochloride salt of the
title compound as a hygroscopic pale-yellow powder (0.25g) mp = 140-145°C.
¹H NMR δ_H (200 MHz; (CD₃)₂SO) 0.8 - 1.8 (10H, m) and 2.3 (1H, m) (cyclohexyl); 2.0
(1H, m), 2.4 (1H, m), 3.0 - 3.8 (4H, m) and 3.9 (1H, m) (tetrahydroquinoline); 2.85 (3H,
br. s, NMe); 3.0 - 3.8 (2H, m) and 4.15 (2H, m) (NCH₂CH₂N); 7.45 (1H, dd, pyridine
30 H5); 7.63 (1H, d, pyridine H3); 7.85 (1H, dd, tetrahydroquinoline H3); 8.00 (1H, dt,
pyridine H4); 8.34 (1H, d, tetrahydroquinoline H4); 8.63 (1H, dd, pyridine H6); and 8.70
(1H, d, tetrahydroquinoline H2).

CLAIMS

1. A compound of general formula



or a pharmaceutically acceptable salt thereof

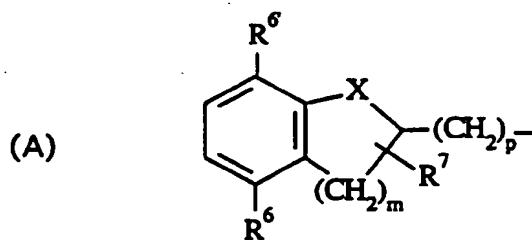
wherein

R¹ is a mono or bicyclic heteroaryl radical,

R² is cycloalkyl,

R³, R^{3'} and R⁴ each represent hydrogen or lower alkyl,

and R⁵ is a group of formula



where X is $-(\text{CH}_2)_n-$, $-\text{OCH}_2-$ or $-\text{SCH}_2-$, m is 0 or 1, n is 1, 2 or 3 and p is 0 or 1 such that $(m + p)$ is 1 and that $(m + n)$ is 1, 2 or 3,

R⁶ is hydrogen, lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl, (lower)alkoxycarbonyl, carboxamido, nitro, cyano, amino, (lower)alkylamino, di(lower)alkylamino or (lower) alkylcarbonyl,

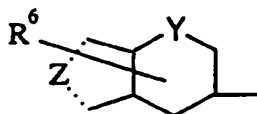
R^{6'} is hydrogen or halogen when X is $-(\text{CH}_2)_n-$ and R^{6'} is hydrogen when X is $-\text{OCH}_2-$ or $-\text{SCH}_2-$,

-16-

R⁷ is hydrogen or lower alkyl

or

(B)



where Y is -O-, -S- or -CH₂-,

Z represents a heteroaromatic ring fused on to the non-aromatic ring containing the Y group

and R⁶ is as defined above and one or more R⁶ groups may be attached to the heteroaromatic ring and/or the non-aromatic ring

or

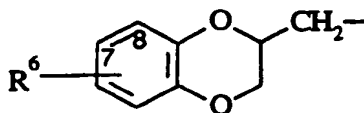
(C)



where R⁸ is a monocyclic or bicyclic heteroaryl group

or

(D)



where R⁶ is as defined above and the indicated 7, 8 positions may optionally be fused with a heteroaromatic ring or a further aromatic ring

or

(E)



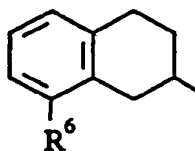
where R⁹ is a mono or bicyclic aryl or bicyclic heteroaryl group

or



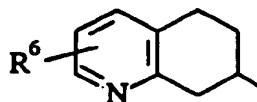
where R^9 is as defined above.

2. A compound as claimed in claim 1 wherein R^5 is a group of formula

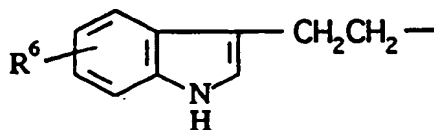


(where R^6 is as defined in claim 1).

3. A compound as claimed in claim 1 wherein R^5 is a group of formula

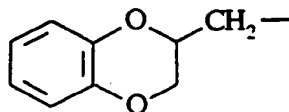


4. A compound as claimed in claim 1 wherein R^5 is a group of formula

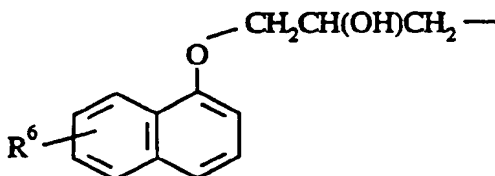


(where R^6 is as defined in claim 1).

5. A compound as claimed in claim 1 wherein R^5 is a group of formula

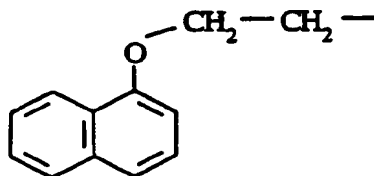


6. A compound as claimed in claim 1 wherein R^5 is a group of formula



(where R^6 is as defined in claim 1).

7. A compound as claimed in claim 1 wherein R^5 is a group of formula



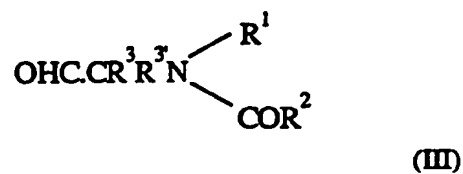
8. A compound as claimed in claim 1 which is
 N-(3-(N'-(1,2,3,4-tetrahydro-8-methoxynaphth-2-yl)methylamino)-2-propyl)-N-(2-pyridinyl)cyclohexanecarboxamide or
 N-(3-(N'-(5,6,7,8-tetrahydroquinolin-7-yl)methylamino)-2-propyl)-N-(2-pyridinyl)cyclohexanecarboxamide or
 N-(3-(N'-(2-(3-(5-methoxyindolyl)ethyl))methylamino)-2-propyl)-N-(2-pyridinyl)cyclohexanecarboxamide or
 N-(3-(2-(2,3-dihydro-1,4-benzodioxinyl)methylamino)-2-propyl)-N-(2-pyridinyl)cyclohexanecarboxamide or
 N-(4-aza-6-hydroxy-7-(1-naphthyloxy)-2-heptyl)-N-(2-pyridinyl)cyclohexanecarboxamide or
 N-(4-aza-6-(1-naphthyloxy)-4-propyl-2-hexyl)-N-(2-pyridinyl)cyclohexanecarboxamide or
 N-(2-(N'-(2-(2,3-dihydro-1,4-benzodioxinyl)methyl)methylamino)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide or
 N-(2-(N'-(7-(5,6,7,8-tetrahydroquinolinyl))methylamino)ethyl)-N-(2-pyridinyl)cyclohexanecarboxamide
 or a pharmaceutically acceptable acid addition salt thereof.

9. A process for preparing a compound claimed in claim 1 which comprises

(a) reductively aminating a compound of formula



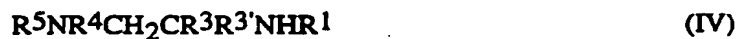
(where R^4 and R^5 are as defined in claim 1) with an aldehyde of formula



(where R^1 , R^2 , R^3 and $R^{3'}$ are as defined in claim 1)

or

(b) acylating an amine of formula



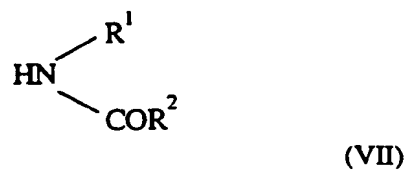
(where R^1 , R^3 , $R^{3'}$, R^4 and R^5 are as defined in claim 1) with an acid of formula



(where R^2 is as defined in claim 1) or with an acylating derivative thereof

or

(c) alkylating an amide of formula



-20-

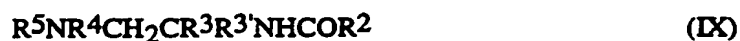
(where R¹ and R² are as defined in claim 1) with an alkylating agent providing the group



(where R³, R^{3'}, R⁴ and R⁵ are as defined in claim 1)

or

(d) heteroarylation of a compound of formula



(where R², R³, R^{3'}, R⁴ and R⁵ are as defined in claim 1) with a compound providing the heteroaryl group R¹

or

(e) converting a base claimed in claim 1 into a pharmaceutically acceptable salt or converting a pharmaceutically acceptable salt into the free base.

10. A pharmaceutical composition comprising a compound claimed in any one of claims 1 to 8 in association with a pharmaceutically acceptable carrier.

11. A compound claimed in any one of claims 1 to 8 for use as a pharmaceutical.

12. A compound claimed in any one of claims 1 to 8 for use as a 5-HT_{1A}-antagonist.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 94/00455

A. CLASSIFICATION OF SUBJECT MATTER IPC 5 C07D213/75 A61K31/395 A61K31/44 C07D401/12 C07D405/12		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 5 C07D A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 512 755 (JOHN WYETH & BROTHER LTD.) 11 November 1992 see claims ---	1,12
A	WO,A,92 06082 (JOHN WYETH & BROTHER LTD.) 16 April 1992 see claims ---	1,12
A	EP,A,0 170 213 (MERREL DOW PHARMACEUTICALS INC.) 5 February 1986 * page 11, last paragraph; claims * ---	1,10
A	EP,A,0 367 888 (ISTITUTO LUSO FARMACO D'ITALIA S.P.A.) 16 May 1990 * page 5, line 13-18; claims * -----	1,10
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"B" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">28 April 1994</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">-9. 05. 94</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Van Bijlen, H</div>

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 94/00455

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0512755	11-11-92	AU-B- 645681 AU-A- 1524192 GB-A- 2255337 JP-A- 5170743	20-01-94 05-11-92 04-11-92 09-07-93
WO-A-9206082	16-04-92	AU-B- 645853 AU-A- 8654491 EP-A- 0502169 GB-A- 2248449 JP-T- 5502682	27-01-94 28-04-92 09-09-92 08-04-92 13-05-93
EP-A-0170213	05-02-86	AU-B- 578962 AU-A- 4535385 CA-A- 1244418 JP-A- 61246180 US-A- 4612312	10-11-88 06-02-86 08-11-88 01-11-86 16-09-86
EP-A-0367888	16-05-90	US-A- 4948797	14-08-90